IN THE SPECIFICATION

Please amend the specification in accordance with the following replacement paragraph written in clean form.

Please delete the paragraph beginning immediately after the title on page 1 and insert the following replacement paragraph:

Cross-Reference to Related Applications

This application is a continuation of co-pending United States Patent Application Serial No. 10/722,184 filed on November 25, 2003, which is a continuation of United States Patent Application Serial No. 10/054,350 (Now U.S. Patent No. 6,699,885), filed on January 19, 2002, which is a continuation-in-part of United States Patent No. 6,645,988, filed on July 9, 2001, which is a continuation-in-part of United States Patent No. 6,489,346, filed on January 11, 2000, which is a continuation-in-part of United States Patent Application No. 09/183,422, filed on October 29, 1998 (now abandoned), which is a continuation-in-part of United States Patent No. 5,840,737, filed on July 15, 1996, which claims priority to United States Provisional Patent Application Serial No. 60/009,608, filed on January 4, 1996. This application claims priority to all such previous applications and patents, and all such applications and patents are hereby incorporated by reference herein.

Please replace the paragraph beginning on page 2, line 22, with the following rewritten paragraph:

-- Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, *Pathogenesis, Diagnosis and Treatment of Acute Gastric Mucosa Lesions,* CLIN GASTROENTEROL 13: 635-650 (1984)). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., *The Prevention of Gastrointestinal Tract Bleeding in Patients in an Intensive Care Unit,* SURG. GYNECOL. OBSTET., 153: 214-220 (1981); Larson et al., *Gastric*

Response to Severe Head Injury, AM. J. SURG. 147: 97-105 (1984); Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History,* N ENGL. J. MED, 291: 925-929 (1974); Skillman et al., *Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated with Lethal Hemorrhage From Acute Stress Ulceration,* AM. J. SURG., 117: 523-530 (1969); and Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients,* N. ENGL. J. MED., 330:377-381 (1994)). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients,* N. ENGL. J. MED., 330:377-381 (1994)). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., *Continuous Intravenous [cimetidine]* Cimetidine *Decreases Stress-related Upper Gastro-intestinal Hemorrhage Without Promoting Pneumonia,* CRIT. CARE MED., 21: 19-30 (1993)). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History,* N ENGL. J. MED, 291: 925-929 (1974); Peura and Johnson, *Cimetidine for Prevention and Treatment of Gastroduodenal Mucosal Lesions in Patients in an Intensive Care Unit,* ANN INTERN MED., 103: 173-177 (1985)). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.--

Please replace the paragraph beginning on page 11, line 18, with the following rewritten paragraph:

-- Second, because bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their reflux disease as the belching can cause upward movement of stomach acid (~~Brunton~~ Goodman AG, et al., *Agents for the Control of Gastric Acidity and Treatment of Peptic Ulcers,* ~~[[IN,]]~~ in THE PHARMACOLOGIC BASIS OF THERAPEUTICS (New York, p. 907 (1990)).--

Please delete the references to Figures 5 – 8 appearing at lines 17 – 23 of page 16.

Please delete the paragraph beginning at page 16, line 24 and replace it with the following amended paragraph:

--Figure ~~9~~ 6 is a graph illustrating the environmental pH values after administration of the proton pump inhibiting agent/buffer formulation.--

Please replace the paragraph beginning on page 43, line 14, with the following rewritten paragraph:

Non-limiting examples of buffering agents which could be utilized in such tablets include sodium bicarbonate, alkaline earth ~~[alkali earth]~~ metal salts such as calcium carbonate, calcium hydroxide, calcium lactate, calcium glycerophosphate, calcium acetate, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum hydroxide or aluminum magnesium hydroxide. A particular alkaline earth ~~[alkali earth]~~ metal salt useful for making an antacid tablet is calcium carbonate.

Please replace the paragraph beginning on page 43, line 20, with the following rewritten paragraph:

An example of a low density alkaline earth ~~[alkali earth]~~ metal salt useful for making the granules according to the present invention is extra light calcium carbonate available from Specialty Minerals Inc., Adams, Me. The density of the extra light calcium carbonate, prior to being processed according to the present invention, is about 0.37 gm/ml.

Please replace the paragraph beginning on page 43, line 25, with the following rewritten paragraph:

The granules used to make the tablets according to one embodiment of the present invention are made by either spray drying or pre-compacting the raw materials. Prior to being processed into granules by either process, the density of the alkaline earth ~~[alkali earth]~~ metal salts useful in the present invention ranges from about 0.3 gm/ml to about 0.55 gm/ml, preferably

about 0.35 gm/ml to about 0.45 gm/ml, even more preferably about 0.37 gm/ml to about 0.42 gm/ml.

Please replace the paragraph beginning on page 57, line 22, with the following rewritten paragraph:

-- Children are affected by gastroesophageal reflux disease (GERD) with atypical manifestations. Many of these atypical symptoms are difficult to control with traditional drugs such as H_2-antagonists, cisapride, or sucralfate. PPIs are more effective in controlling gastric pH and the symptoms of GERD than other agents. However, PPIs are not available in dosage forms that are easy to administer to young children. To address this problem, applicant employed omeprazole or lansoprazole in a buffered chocolate suspension ~~(Choco-Base)~~ (Choco-Base™) in children with manifestations of GERD.--

Please replace the paragraph beginning on page 58, line 5, with the following rewritten paragraph:

-- Applicant performed a retrospective evaluation of children with GERD referred to the University of Missouri-Columbia from 1995 to 1998 who received treatment with the experimental omeprazole or lansoprazole ~~Choco-Base~~ Choco-Base™ suspension formulated in accordance with Formulation 1 stated below. Data were included on all patients with follow up information sufficient to draw conclusions about pre/post treatment (usually > 6 months). There were 25 patients who met the criteria for this evaluation. Age range was several weeks to greater than 5 years. Most patients had a history of numerous unsuccessful attempts at ameliorating the effects of GERD. Medication histories indicated many trials of various drugs.--

Please replace the paragraph beginning on page 59, line 13, with the following rewritten paragraph:

--Of the 24 remaining patients, 18 were males and 6 were females. Ages at implementation of PPI therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months [mean of 37 mo.] Early on, reflux was usually documented by endoscopy and confirmed by pH probe. Eventually, pH probe was dropped and endoscopy was the sole method for documenting reflux, usually at the time of another surgery (most often T-

tubes or adenoidectomy). Seven patients had pH probe confirmation of GERD, whereas 18 had endoscopic confirmation of reflux including all eight who had pH probing done (See Graphs 1 and 2 below). Reflux was diagnosed on endoscopy most commonly by cobblestoning of the tracheal wall, with laryngeal and pharyngeal cobblestoning as findings in a few patients. Six patients had neither pH nor endoscopic documentation of GERD, but were tried on PPI therapy based on symptomatology alone.--

Please replace the paragraph beginning on page 60, line 18, with the following rewritten paragraph:

--The proton pump inhibitor suspension used in this group of patients was ~~Choco-Base~~ Choco-Base™ suspension of either lansoprazole or omeprazole. The dosing was very uniform, with patients receiving doses of either 10 or 20 mg of omeprazole and 23 mg of lansoprazole. Initially, in April of 1996 when therapy was first instituted 10 mg of omeprazole was used. There were 3 patients in this early phase who were treated initially with 10 mg po qd of omeprazole. All three subsequently were increased to either 20 mg po qd of omeprazole or 23 mg po qd of lansoprazole. All remaining patients were given either the 20 mg omeprazole or the 23 mg lansoprazole treatment qd, except in one case, where 30 mg of lansoprazole was used. Patients were instructed to take their doses once per day, preferably at night in most cases. Suspensions were all filled through the University of Missouri Pharmacy at Green Meadows. This allowed for tracking of usage through refill data.--

Please replace the paragraph beginning on page 61, line 7, with the following rewritten paragraph:

-- Most patients responded favorably to and tolerated the once daily dosing of ~~Choco-Base~~ Choco-Base™ proton pump inhibitor suspension. Two patients had documented adverse effects associated with the use of the PPI suspension. In one patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment failure. The other patient had small amounts of bloody stools per mother. This patient never had his stool tested, as his bloody stool promptly resolved upon cessation of therapy, with no further sequellae. The other 23 patients had no documented adverse effects.—

Please replace the paragraph beginning on page 61, line 14, with the following rewritten paragraph:

Patients were categorized based on review of clinic notes and chart review into general categories: (1) improved; (2) unchanged; (3) failed; and (4) inconclusive. Of 24 patients with sufficient data for follow up, 18 showed improvement in symptomatology upon commencement of PPI therapy [72%]. The seven who did not respond were analyzed and grouped. Three showed no change in symptomatology and clinical findings while on therapy, one complained of worsening symptoms while on therapy, one patient had therapy as prophylaxis for surgery, and two stopped therapy just after its commencement (see graph 4). Setting aside the cases in which therapy was stopped before conclusions could be drawn and the case in which PPI therapy was for purely prophylactic reasons, leaves (17/21) 81% of patients that responded to ~~Choco-Base~~ Choco-Base™ suspension. This means that 19% (4/21) of patients received no apparent benefit from PPI therapy. Of all these patients, only 4% complained of worsening symptoms and the side effects were 4% (1/21) and were mild bloody stool that completely resolved upon cessation of therapy.

Please replace the paragraph beginning on page 62, line 13, with the following rewritten paragraph:

The standard of therapy for the treatment of GERD in the pediatric population has become a progression from conservative therapy to a combination of a pro-kinetic agent and H-2 blocker therapy. Nonetheless, many patients fail this treatment protocol and become surgical candidates. In adults, PPI therapy is effective in 90% of those treated for gastroesophageal reflux disease. As a medical alternative to the H-2 blockers, the proton pump inhibitors have not been studied extensively in the pediatric population. Part of the reason for this lack of data may be related to the absence of a suitable dosage formulation for this very young population, primarily under 2 years of age, that does not swallow capsules or tablets. It would be desirable to have a true liquid formulation (solution or suspension) with good palatability such as is used for oral antibiotics, decongestants, antihistamines, H-2 blockers, cisapride, metoclopramide, etc. The use of lansoprazole granules (removed from the gelatin capule) and sprinkled on applesauce has been approved by the Food and Drug Administration as an alternative method of drug administration in adults but not in children. Published data are lacking on the efficacy of the lansoprazole

sprinkle method in children. Omeprazole has been studied for bioequivalence as a sprinkle in adults and appears to produce comparable serum concentrations when compared to the standard capsule. Again no data are available on the omeprazole sprinkle in children. An additional disadvantage of omeprazole is its taste which is quinine-like. Even when suspended in juice, applesauce or the like, the bitter nature of the medicine is easily tasted even if one granule is chewed. For this reason applicant eventually progressed to use lansoprazole in Choco-Base™ ~~Choco-Base~~. Pantoprazole and rabeprazole are available as enteric-coated tablets only. Currently, none of the proton pump inhibitors available in the United States are approved for pediatric use. There is some controversy as to what the appropriate dosage should be in this group of patients. A recent review by Israel D., et al. suggests that effective PPI dosages should be higher than that originally reported, i.e., from 0.7 mg/kg to 2 or 3 mg/kg omeprazole. Since toxicity with the PPI's is not seen even at >50mg/kg, there appears little risk associated with the higher dosages. Based on observations at the University of Missouri consistent with the findings of this review, applicant established a simple fixed dosage regimen of 10ml Choco-Base™ ~~Choco-Base~~ suspension daily. This 10ml dose provided 20mg omeprazole and 23 mg lansoprazole.

Please replace the paragraph beginning on page 64, line 5, with the following rewritten paragraph:

Choco-Base™ ~~Choco-Base~~ is a product which protects drugs which are acid labile, such as proton pump inhibitors, from acid degradation. The first few pediatric patients with reflux prescribed Choco-Base™ ~~Choco-Base~~ were sicker patients. They had been on prior therapy and had been diagnosed both by pH probe and endoscopy. In the first few months, applicant treated patients with 10 mg of omeprazole qd (1 mg/kg) and found this to be somewhat ineffective, and quickly increased the dosing to 20 mg (2 mg/kg) of omeprazole. About halfway through the study, applicant began using lansoprazole 23 mg po qd. Applicant's standard therapy was then either 20 mg of omeprazole or 23 mg of lansoprazole once daily. The extra 3 mg of lansoprazole is related only to the fact that the final concentration was 2.25 mg/ml, and applicant desired to keep dosing simple, so he used a 10 ml suspension.

Please replace the paragraph beginning on page 66, line 21, with the following rewritten paragraph:

--The Choco-Base™ ~~Choco-Base~~ product is formulated as follows:--

Please replace the paragraph beginning on page 69, line 7, with the following rewritten paragraph:

-- In all four of the above formulations, lansoprazole or other PPI can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200 mg of omeprazole. Additionally, aspartame can be substituted for sucrose, and the following other ingredients can be employed as carriers, adjuvants and excipients: maltodextrin, vanilla, carragreenan, mono and diglycerides, and lactated monoglycerides. One skilled in the art will appreciate that not all of the ingredients are necessary to create a Choco-Base™ ~~Choco-Base~~ formulation that is safe and effective.--

Please replace the paragraph beginning on page 70, line 5, with the following rewritten paragraph:

--Applicant additionally analyzed the effects of a lansoprazole Choco-Base™ ~~Choco-Base~~ formulation on gastric pH using a pH meter (Fisher Scientific) in one adult patient versus lansoprazole alone. The patient was first given a 30 mg oral capsule of Prevacid®, and the patient's gastric pH was measured at 0, 4, 8, 12, and 16 hours post dose. The results are illustrated in Fig. 4.--

Please replace the paragraph beginning on page 70, line 10, with the following rewritten paragraph:

-- The Choco-Base™ ~~Choco-Base~~ product was compounded according to Formulation 1 above, except 300 mg of lansoprazole was used instead of omeprazole. A dose of 30 mg lansoprazole Choco-Base™ ~~Choco-Base~~ was orally administered at hour 18 post lansoprazole alone. Gastric pH was measured using a pH meter at hours 18, 19, 24, 28, 32, 36, 40, 48, 52, and 56 post lansoprazole alone dose.--

Please replace the paragraph beginning on page 86, line 19, with the following rewritten paragraph:

--(b) 20 mg of a liquid formulation of approximately 2 mg omeprazole per 1 ml of 8.4% sodium bicarbonate[.];--

Please replace the paragraph beginning on page 88, line 6, with the following rewritten paragraph:

--Blood samples will be centrifuged within 2 hours of collection and the plasma will then be separated and frozen at –10° C (or lower) until assayed. Pharmacokinetic variables will include: time to peak concentration, mean peak concentration, AUC (0-t) and (0-infinity). Analysis of variance will be used to detect statistical difference. Bioavailability will be assessed by the 90% confidence interval of the two one-sided tests on the natural logarithm of AUC.--

Please replace the paragraph beginning on page 88, line 16, with the following rewritten paragraph:

-- Omeprazole and internal standard (H168/24) will be used. Omeprazole and internal standard will be measured by modification of the procedure described by Amantea and Narang. (Amantea MA, Narang PK. Improved Procedure for Quantification of Omeprazole and Metabolites Using Reversed-Phased High Performance Liquid Chromotography. J. CHROMATOGRAPHY 426; 216-222. 1988). Briefly, ~~20ul~~ 20 µl of omeprazole 2mg/ml NaHCO3 or Choco-Base™ ~~Choco-Base~~ omeprazole suspension and ~~100 ul~~ 100 µl of the internal standard are vortexed with ~~150 ul~~ 150 µl of carbonate buffer (pH=9.8), 5 ml of dichloroethane, 5 ml of hexane, and ~~980 ul~~ 980 µl of sterile water. After the sample is centrifuged, the organic layer is extracted and dried over a nitrogen stream. Each pellet is reconstituted with ~~150 ul~~ 150 µl of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 µl is injected onto a C18 5 U column equilibrated with the same mobile phase at 1.1ml/min. Under these conditions, omeprazole is eluted at approximately 5 minutes, and the internal standard at approximately 7.5 minutes. The standard curve is linear over the concentration range 0-3 mg/ml (in previous work with SOS), and the between-day coefficient of variation has been <8% at all concentrations. The typical mean R2 for the standard curve has been 0.98 in prior work with SOS (omeprazole 2mg/ml NaHCO3 8.4%).--

Please replace the paragraph beginning on page 90, line 10, with the following rewritten paragraph:

-- A suspension was prepared by mixing 8.4% sodium bicarbonate with omeprazole to produce a final concentration of 2 mg/ml to determine the stability of omeprazole solution after 12 months. The resultant preparation was stored in clear glass at room temperature, refrigerated and frozen. Samples were drawn after thorough agitation from the stored preparations at the prescribed times. The samples were then stored at 70°C. Frozen samples remained frozen until they were analyzed. When the collection process was completed, the samples were shipped to a laboratory overnight on dry ice for analysis. Samples were agitated for 30 seconds and sample aliquots were analyzed by HPLC in triplicate according to well known methods. Omeprazole and the internal standard were measured by a modification of the procedure described by Amantea and Narang. Amantea MA, Narang PK, Improved Procedure For Quantitation Of Omeprazole And Metabolites Using Reverse-Phased High-Performance Liquid Chromatography, J. Chromatography, 426: 216-222 (1988). ~~Twenty (20) ul~~ Twenty (20) µl of the omeprazole 2mg/ml NaHCO3 solution and ~~100 ul~~ 100 µl of the internal standard solution were vortexed with ~~150 ul~~ 150 µl of carbonate buffer (pH = 9.8), 5 ml dichloroethane, 5 ml hexane, and ~~980 ul~~ 980 µl of sterile water. The sample was centrifuged and the organic layer was extracted and dried over a nitrogen stream. Each pellet was reconstituted with ~~150 ul~~ 150 µl of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, ~~75 ul~~ 75 µl were injected onto a C185u column equilibrated with the same mobile phase at 1.1 ml/min. Omeprazole was eluted at ~5 min, and the internal standard at ~7.5 min. The standard curve was linear over the concentrated range 0-3 mg/ml, and between-day coefficient of variation was < 8% at all concentrations. Mean R2 for the standard curve was 0.980.--